REMARKS

The present invention relates in part to the use of affinity tags in recombinant fusion protein constructs. In particular, the claimed invention relates to affinity tags which comprise two or more modules capable of mediating binding to streptavidin.

Prior to the present submission, claims 16, 17, 32–34, 36, 37, 41–45, and 47-51 are pending in the application, with claims 16, 17, 32–34, 36, 37, 40–45, and 47-51 under examination. The balance of the claims has been withdrawn from examination by the Examiner in accordance with a restriction requirement.

By the present submission, claim 16 (the sole independent claim under examination) is amended to incorporate the limitations of claims 7 and 41 and language concerning the length of each binding module being 3 to 15 amino acids. Applicants note that claim 41 (which depended from claim 16) was not subject to any rejection in the Office Action.

Exemplary support for these amendments may be found in the final paragraph of page 13 of the specification and in the originally filed claims. Claim 41 is cancelled herein. No new matter is introduced by these amendments. Notwithstanding the foregoing, Applicant expressly reserves the right to prosecute subject matter no longer or not yet claimed in one or more applications that may claim priority to the present application.

Reconsideration of the claimed invention is respectfully requested in view of the amendments and remarks contained herein.

I. Rejection Under 35 U.S.C. §112, First Paragraph

The rejection of claims 16, 37, and 49-51 as allegedly failing to satisfy the written description requirement is respectfully traversed.

The claimed invention relates to provision of a fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest. As recited in claim 16, the streptavidin–binding peptide comprises a sequential arrangement of two modules with an amino acid sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine. At least one of the modules comprises a sequence –Oaa–Xaa–His–Pro–Gln–Phe–Yaa–Zaa– (SEQ ID NO:7), where Oaa is Trp, Lys or Arg, Xaa is any amino acid and where either Yaa and Zaa are both Gly or Yaa is Glu and Zaa is Lys or Arg. The

streptavidin–binding peptide is located at the carboxy terminal end or at the amino terminal end of the protein sequence to which it is fused.

Applicants note that claim 16, the only independent claim under examination, now incorporates the limitations of claim 41, which was not subject to any rejection in the Office Action.

As to the merits of the rejection, the statement on page 3 of the Office Action that "the claimed invention is directed to said streptavidin mutein for example fused to any full length protein" is in error, as are similar statements on pages 7 and 8 in the "Response to Arguments" section of the Office Action. The claimed invention is not directed to a "streptavidin mutein." It is directed to a short peptide tag sequence which binds to streptavidin or certain streptavidin muteins. Thus, the remarks in the "Response to Arguments" section of the Office Action, largely directed to such "streptavidin muteins," are not pertinent to the written description of the claimed invention.

The Office Action takes the position that the claimed invention represents a "large variable genus" and that, for example, "there is no indication of what a structure with a mutein having 5 modules looks like." Office Action, page 4. Beyond continuing to apparently confuse the claimed invention with "streptavidin muteins," Applicant respectfully disagrees with the premise of the assertion. As indicated in the claims, a structure having 5 modules would be as follows:

> each of the modules is 3 to 15 amino acids in length and comprises an amino acid sequence –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine;
>
> at least one of the modules comprises a sequence –Oaa–Xaa–His–Pro–Gln–Phe–Yaa–Zaa– (SEQ ID NO:76), where Oaa is Trp, Lys or Arg, Xaa is any amino acid and where either Yaa and Zaa are both Gly or Yaa is Glu and Zaa is Lys or Arg; and
>
> the spacing between individual modules is 0 to 50 amino acids.

Applicant submits that the skilled artisan would readily understand what the structure having 5 modules "looks like" based on the claims and the specification.

Moreover, the claim also provides functional characteristics coupled to the claimed structure. The claimed invention is a "fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest." The modules of the claims refer to the structure of the "streptavidin–binding peptide" and correlate the structure with the streptavidin–binding function.

Applicant respectfully submits that the rejection does not set forth a proper basis for rejecting the claimed invention under the written description requirement. The Office Action refers to a written description requiring "more than a mere statement that it is part of the invention and a reference to a potential method of isolating it." Office Action, page 5. This language from *Fiers v. Revel* refers to a case in which a claim was made to a DNA sequence coding for human beta-interferon, where the applicants did not possess the structure of that sequence. In the present case, Applicant plainly had the structure of the streptavidin–binding peptides of the claims at the time the present application was filed, together with the understanding that the claimed fusion proteins have the streptavidin–binding peptide "affinity tag" located at the amino and/or carboxyl terminus of a protein sequence of interest.

Applicant has previously presented a declaration of Dr. Thomas Schmidt, which discusses in some detail the understanding in the art regarding the use of affinity tags as part of a fusion protein. Dr. Schmidt refers to Ford *et al., Prot. Expr. Purific.*, 2, 95–107, 1991 for a review of the field regarding fusion tags as it stood more than a decade before the filing date of the present invention. As described therein, "fusion tail systems have been developed to promote efficient recovery and purification of recombinant proteins from crude cell extracts or culture media. In these systems, a target protein is genetically engineered to contain a C- or N-terminal polypeptide tail, which provides the biochemical basis for specificity in recovery and purification." Ford *et al.*, Abstract. Such affinity tags "have been designed for fusion to virtually any target protein that can be cloned and expressed in a microbial host." Ford *et al.*, page 95, right column (emphasis added). As noted in Fig. 1 of Ford *et al.*, affinity for the binding partner of the affinity tag is provided by the affinity tag itself; the remainder of the fusion protein is largely irrelevant to this interaction. Schmidt declaration, paragraphs 5 and 6. The skilled artisan understands that the binding characteristics of the fusion protein to streptavidin are determined by the structure of the affinity tag, not the polypeptide sequence of interest to which the affinity tag is linked.

Ford *et al.* unambiguously corroborates Dr. Schmidt's conclusion that, as of the priority date of the present application (March 12, 2001), it was within the knowledge of the person of average skill in the field of recombinant protein production to construct an expression vector in which a affinity tag fused on the DNA level C-terminally or N-terminally to a protein of interest and then produce this fusion protein in a suitable expression system. See also, in this regard, U.S. patents 5,506,121 and 6,103,493, and the previously submitted review article of Schmidt & Skerra, *Meth. Enzymol.*, Vol. 326, pages 271-304, 2000. The present invention is directed to new affinity tags that may be used in such methods.

The Office Action asserts that this argument is "not convincing," because the tag might have several modules and "[t]he protein partner is important since binding might not occur depending on the fragment or variant thereof." Office Action, page 8, last paragraph. These assertions, however, are contrary to the evidence of record (*e.g.*, the specification, the Schmidt declaration and Ford *et al.*). The Office Action offers no basis for the assertions, which appear to be nothing more than personal opinion of unpredictability, and which amount to nothing more than hypothetical scenarios -- that certain embodiments might be inoperable. A general allegation of unpredictability is not a sufficient ground to support a rejection for lack of written description. MPEP 2163.04(I).

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. See MPEP § 2163.02 (citing Ralston Purina Co. v. Far-Mar-Co., Inc., 227 USPQ 177, 179 (Fed. Cir. 1985)). An adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a) (emphasis added).

Applicant respectfully submits that the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. Because the written description requirement demands no more, Applicant requests that the rejection be reconsidered and withdrawn.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

The rejection of claim 36 as allegedly not satisfying the definiteness requirement is respectfully traversed.

The rejection takes the position that claim 16 requires that each module comprises the sequence His–Pro–Baa where Baa is glutamine, asparagines, and methionine, and at least one module "is His–Pro–Gln–Phe." Applicant notes that this is an incorrect statement of the claims; the claims (prior to the present amendment) state that at least one module comprises the sequence His–Pro–Gln–Phe, not that it is His–Pro–Gln–Phe. The rejection further states that claim 34 (Applicants believe that claim 36 is intended) "indicates that each module has to be His-Pro-Gln." Applicant again notes that this is an incorrect statement of the claims; claim 36 states that each module comprises a sequence –His–Pro–Gln–. A module that comprises the sequence His–Pro–Gln–Phe also comprises the sequence –His–Pro–Gln–.

Applicant requests that the rejection be reconsidered and withdrawn.

III. REJECTION UNDER 35 U.S.C. §102(e)

The rejection of claims 16, 17 and 48 under 35 U.S.C. §102(e) as allegedly being anticipated by Ley *et al.*, U.S. Patent No. 6,906,176, is respectfully traversed.

The claimed invention relates to provision of a fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest. As recited in claim 16, the streptavidin–binding peptide comprises a sequential arrangement of at least two modules with an amino acid sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine.

The claim as amended herein further specifies that at least one of the modules comprises a sequence –Oaa–Xaa–His–Pro–Gln–Phe–Yaa–Zaa– (SEQ ID NO:7), where Oaa is Trp, Lys or Arg, Xaa is any amino acid and where either Yaa and Zaa are both Gly or Yaa is Glu and Zaa is Lys or Arg. Ley *et al.* discloses no such fusion proteins. Applicants note that claim 16, the only independent claim under examination, now incorporates the limitations of claim 41, which was not subject to any rejection in the Office Action.

In order to establish a *prima facie* case of anticipation, the Examiner bears the burden of demonstrating that each and every limitation of the claimed methods is present in the cited

reference. In this case, the Examiner has not met that burden. Because no *prima facie* case of anticipation has been established, Applicant requests that the rejection be reconsidered and withdrawn.

IV. REJECTION UNDER 35 U.S.C. §102(e)

The rejection of claims 16, 17, 32, and 41 under 35 U.S.C. §102(e) as allegedly being anticipated by Szostak *et al.*, U.S. Patent No. 6,841,359 is respectfully traversed.

The claimed invention relates to provision of a fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest. As recited in claim 16, the streptavidin–binding peptide comprises a sequential arrangement of two modules with an amino acid sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine. At least one of the modules comprises a sequence –His–Pro–Gln–Phe–.

By contrast, the '359 patent fails to disclose the use of a module comprising a sequence –His–Pro–Gln–Phe–. The Office Action points to "SEQ ID NO:25; having '-His-Pro-Gln-Phe-' moiety with a specific dissociation constant" in support of the rejection. Office Action, page 9. Applicants note, however, that SEQ ID NO: 25 contains no such '-His-Pro-Gln-Phe-' sequence.

Moreover, as discussed by Dr. Schmidt in paragraph 11 of his declaration, the '359 patent informs the artisan in column 15, lines 63-66, that the presence of two HPQ (His–Pro–Gln) motifs does not confer high affinity binding to streptavidin. And, in column 10, lines 12-24, the '359 patent states that binding to streptavidin is actually conferred by the entirety of a 38 residue peptide. Thus, claim 1 of the '359 patent refers to "[a] peptide which binds streptavidin with a dissociation constant less than 10 μM and comprises an amino acid sequence having at least 80% identity to the first 38 amino acids of SEQ ID NO:25." Given this, Applicants submit that the '359 patent plainly does not disclose the claimed fusion proteins which comprise a sequential arrangement of two specified modules.

In order to establish a *prima facie* case of anticipation, the Examiner bears the burden of demonstrating that each and every limitation of the claimed methods is present in the cited reference. In this case, the Examiner has not met that burden. Because no prima facie case of

anticipation has been established, Applicant requests that the rejection be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth herein, Applicant respectfully submits that claims 16, 17, 32–34, 36, 37, 42–45, and 47-51 are in condition for allowance. Applicants respectfully request that the Examiner reconsider and withdraw the grounds for rejection set forth in the Office Action. Applicant further requests that, in the event the Examiner agrees that the product claims under examination are in allowable form, the corresponding method claims 19-22 be rejoined in accordance with the requirement for restriction issued June 17, 2004.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (619) 203-3186.

Respectfully submitted,

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Date: 10 February 2010

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